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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/719,311	11/20/2003	John A. Chiorini	14014.0252U3	3284
36339 7590 09/18/2007 NATIONAL INSTITUTE OF HEALTH C/O NEEDLE & ROSENBERG, P.C. SUITE 1000 999 PEACHTREE STREET ATLANTA, GA 30309			EXAMINER KAUSHAL, SUMESH	
			ART UNIT 1633	PAPER NUMBER
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary

Application No.

10/719,311

Applicant(s)

CHIORINI ET AL.

Examiner

Sumesh Kaushal

Art Unit

1633

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 23 July 2007.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 2,3,6-28 and 30-42 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 2-3, 6-28 and 30-42 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- 1) ☐ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☐ Information Disclosure Statement(s) (PTO/SB/08)
Paper No(s)/Mail Date _____
- 4) ☐ Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____
- 5) ☐ Notice of Informal Patent Application
- 6) ☐ Other: _____

DETAILED ACTION

Applicant's response filed on 07/23/07 has been acknowledged and fully considered.

Claims 2-3, 6-28, 30-42 are pending and are examined in this office action.

Applicants are required to follow Amendment Practice under revised 37 CFR §1.121. The fax phone numbers for the organization where this application or proceeding is assigned is 571-273-8300.

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 7/23/07 has been entered.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 2-3, 6-28 and 30-42 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter, which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Art Unit: 1633

The scope instant claims encompasses a vector system that comprises variants of AAV4 capsid protein having about 90% homology to an amino acid sequence set forth in SEQ ID NO:4, and about 98% homology to SEQ ID NO: 4, 16 and 18. In addition the scope of invention as claimed further encompasses variants of AAV4 Rep protein having about 95% homology to amino acid sequences set forth in SEQ ID NO:2, 8, 9, 10 and 11. Besides the nucleotide sequence of SEQ ID NO:1, which encodes the AAV4 genome, the AAV4 Rep proteins (SEQ ID NO(s): 2, 8, 9, 10 and 11) and the AAV4 Capsid proteins (SEQ ID NO(s): 4, 16 and 18) the specification as failed fails to disclose any variants of AAV4 Rep and AAV4 Capsid proteins (as claimed).

Response to Argument (Written description)

The applicant argues that the variants as claimed now has been amended to recite 90% homology instead of 98% which further recites the functional characteristics of "AAV particle production" which is clearly a functional limitation that can be assayed by skilled artisan.

However the applicant's arguments are found not persuasive because the production of AAV particles is the function of entire vector system, which further depends upon the variants of individual components (i.e. Rep and Caspid) eliciting specific protein activity (i.e Rep and Casid protein specific activities). Therefore the variants fails to meet USPTO written description guidelines because the invention as claimed fails to recite any specific functional limitation associated with structural variants as claimed. For example the Rep proteins encompasses Rep40, Rep 52, Rep68 and Rep 78, which are involved in regulation of replication and transcription in addition to the production of single-stranded progeny genome. Furthermore two of the Rep proteins have been associated with the preferential integration of AAV genomes into a region of the q arm of human chromosome 19. Rep68/78 have also been shown to possess NTP binding activity as well as DNA and RNA helicase activities. The Rep proteins possess a nuclear localization signal as well as several potential phosphorylation sites. Mutation of one of these kinase sites resulted in a loss of replication activity. Similarly the capsid protein consists of three related proteins referred to as VP1, 2 and 3. These proteins are found in a ratio of 1:1:10 respectively and are all derived from the right-hand ORF. The

Art Unit: 1633

capsid proteins differ from each other by the use of alternative splicing and an unusual start codon. Deletion analysis has shown that removal or alteration of VP1 which is translated from an alternatively spliced message results in a reduced yield of infectious particles. Mutations within the VP3 coding region result in the failure to produce any single-stranded progeny DNA or infectious particles (see Spec. pages 1-4)

Applicant is referred to the guidelines for *Written Description Requirement* published January 5, 2001 in the Federal Register, Vol.66, No.4, pp.1099-1110. The disclosure of a single species is rarely, if ever, sufficient to describe a broad genus, particularly when the specification fails to describe the features of that genus, even in passing. (see *In re Shokal* 113USPQ283(CCPA1957); *Purdue Pharma L. P. vs Faulding Inc.* 56 USPQ2nd 1481 (CAFC 2000). In analyzing whether the written description requirement is met for the genus claim, it is first determined whether a representative number of species have been described by their complete structure. Next, it is determined whether a representative number of species have been sufficiently described by other relevant identifying characteristics (i.e. conserve motifs or domains).

In the instant case specification fails to disclose representative number of species by structure and function encompassed by the genus as claimed i.e. "any and all functionally equivalent variants of Rep and Capsid proteins. Furthermore the genus as claimed encompasses structurally and functionally distinct members other genus. Claiming all divergent species that achieve a result as contemplated by the application without defining the representative number of species by structure and function is not in compliance with the written description requirement. *Rather, it is an attempt to preempt the future before it has arrived.* "The written description requirement has several policy objectives. The essential goal' of the description of the invention requirement is to clearly convey the information that an applicant has invented the subject matter which is claimed." *In re Barker*, 559 F.2d 588, 592 n.4, 194 USPQ 470, 473 n.4 (CCPA 1977). Another objective is to put the public in possession of what the applicant claims as the invention. See *Regents of the University of California v. Eli Lilly*, 119 F.3d 1559, 1566, 43USPQ2d 1398, 1404 (Fed. Cir. 1997), cert. denied, 523 U.S. 1089 (1998)."

Art Unit: 1633

To satisfy the written description requirement, a patent specification must describe the claimed invention in sufficient detail such that the Artisan can reasonably conclude that the inventor(s) had possession of the claimed invention. Such possession may be demonstrated by describing the claimed invention with all of its limitations using such descriptive means as words, structures, figures, diagrams, and/or formulae that fully set forth the claimed invention. Possession may be shown by an actual reduction to practice, showing that the invention as claimed is "ready for patenting", or by describing distinguishing identifying characteristics sufficient to show that applicant was in possession of the claimed invention (see Fed.Reg., Vo.66, No. 4, pp. 1099-11, January 5, 2001).

Since the specification fails to disclose a representative number of species defined by structure and function, it is not possible to envision the claimed composition. One cannot describe what one has not conceived. (See *Fiddes v. Baird*, 30 USP2d 1481 at 1483). Therefore, the lack of disclosure in the specification is not deemed sufficient to reasonably convey to one skilled in the art that the applicants were in possession of the huge genera recited in the claims at the time the application was filed. Furthermore the possession may be shown by actual reduction to practice, clear depiction of the invention in a detailed drawing, or by describing the invention with sufficient relevant identifying characteristics (as it relates to the claimed invention as a whole) such that a person skilled in the art would recognize that the inventor had possession of the claimed invention. See, e.g., *Pfaff v. Wells Electronics, Inc.*, 525 U.S. 55, 68, 119 S.Ct. 304, 312, 48 USPQ2d 1641, 1647 (1998); *Eli Lilly*, 119 F.3d at 1568, 43 USPQ2d at 1406; *Amgen, Inc. v. Chugai Pharmaceutical*, 927 F.2d 1200, 1206, 18 USPQ2d 1016, 1021 (Fed. Cir. 1991).

In the instant case the nucleic acid sequences as claimed has been defined only by a statement of function that broadly encompasses "any variants of AAV4 capsid protein having about 90% homology to an amino acid sequence set forth in SEQ ID NO:4, and about 98% homology to SEQ ID NO: 4, 16 and 18; and any variants of AAV4 Rep protein having about 95% homology to amino acid sequences set forth in SEQ ID NO:2, 8, 9, 10 and 11 that are capable of producing AAV particle in any vector system",

Art Unit: 1633

which conveyed no distinguishing information about the identity of the claimed genetic material, such as its relevant structural or physical characteristics. Therefore, a definition by function alone "does not suffice" to sufficiently describe a coding sequence "because it is only an indication of what the gene does, rather than what it is." *Eli Lilly*, 119 F.3 at 1568, 43 USPQ2d at 1406. See also *Fiers*, 984 F.2d at 1169-71, 25 USPQ2d at 1605-06 (discussing *Amgen Inc. v. Chugai Pharmaceutical Co.*, 927 F.2d 1200, 18 USPQ2d 1016 (Fed. Cir. 1991)). According to these facts, one skill in the art would conclude that applicant was not in the possession of the claimed genus because a description of even a single member of this genus would not be representative of other variants and is insufficient to support the claim.

Claims 2-3, 6-28 and 30-42 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a vector system for producing infectious AAV4 particles comprising AAV4 capsid proteins (SEQ ID NO: 4, 16 and 18) and AAV4 Rep proteins (SEQ ID NO:2, 8, 9, 10 and 11), does not reasonably provide enablement for any other vector system that comprises any variant of AAV4 Capsid (i.e. SEQ ID NO: 4, 16 and 18) or Rep proteins (i.e. SEQ ID NO:2, 8, 9, 10 and 11) and/or any vector system that only encodes a single Capsid or Rep protein and is capable of producing the AAV particles. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Response to Argument (Enablement)

The applicant argues that the claims have been amended such that AAV4 capsid protein encoded by the vector system is defined structurally by sequence homology and functionally by the ability to produce AAV particles. The applicant further argues that it would not require an undue amount of experimentation to practice the invention as claimed because the skill in the art of engineering viral vectors is high, and based on the very high sequence identity claimed for the AAV4 capsid protein (i.e., 90%), there is a high degree of predictability that any given variant produced by the skilled artisan will have the desired characteristics (e.g., tropism).

Art Unit: 1633

However this is found not persuasive in view of written description rejection above as the specification fails to disclose a representative number of species defined by structure and function (i.e. Capsid and Rep specific functions). Therefore, it is unclear how one skilled in the art use the invention as claimed. The applicant's disclosure does not enable one skilled in the art to practice the invention as claimed without further undue amount. of experimentation, which requires the identification and characterization of any and all variants of AAV4 Capsid (i.e. SEQ ID NO: 4, 16 and 18) or Rep proteins (i.e SEQ ID NO:2, 8, 9, 10 and 11) that are capable of producing the AAV particles alone or in any combination. In instant case applicant only disclosed AAV4 genome (AAV4 2260-4467nt of SEQ ID NO:1), AAV4 Rep proteins (SEQ ID NO(s): 2, 8, 9, 10 and 11) and AAV4 Capsid proteins (SEQ ID NO(s): 4, 16 and 18); and proposes to discover other members of the genus. At issue, under the enablement requirement of 35 U.S.C. 1 12, first paragraph is whether, given the Wands-factors, the experimentation was undue or unreasonable under the circumstances. Experimentation must not require ingenuity beyond that to be expected of one of ordinary skill in the art." See *Fields v. Conover*, 443 F.2d 1386, 170 USPQ 276 (CCPA 1970). It is noted that the unpredictability of a particular area may alone provide reasonable doubt as to the accuracy of the broad statement made in support of enablement of claims. See *Ex parte Singh*, 17 USPQ2d 1714 (BPAI 1991). Therefore considering the state of the art and limited amount of guidance provided in the instant specification, one skill in the art would have to engage in excessive and undue amount of experimentation to exercise the invention as claimed.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 2-3, 6-28, 30-42 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Art Unit: 1633

Claims 2, 17, 19, 21, 23, 25, 32, 3 and 36 are indefinite because instant claim recites claim limitation "about" to describe percent homology. "About" means reasonably close or in the vicinity. Since the term "about" does not exactly defines metes and bounds of the invention as claimed, the terminology does point out the subject matter which applicant regards as the invention.

Claims 32 and 37 are indefinite because these claims depend upon claims that have been canceled (claim 4 and claim 29).


Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sumesh Kaushal whose telephone number is 571-272-0769. The examiner can normally be reached on Mon-Fri. from 9AM-5PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph Woitach can be reached on 571-272-0739. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.


SUMESH KAUSHAL
PRIMARY EXAMINER